TENT COOPERATION TRE

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 21 August 2000 (21.08.00)	
International application No. PCT/AU00/00004	**Applicant's or agent's file reference** FP12072
International filing date (day/month/year) 06 January 2000 (06.01.00)	**Priority date** (day/month/year) 13 January 1999 (13.01.99)
Applicant BROWN, Tracey	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 July 2000 (14.07.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Charlotte ENGER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 00/00004

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[7]: A61K 47/36; A61P 35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: A61K AND KEYWORDS AS INDICATED BELOW

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
AU: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT) (methotrexate, packtaxel, 5-fluorouracil, cyclophosphamide, cancer, cytotoxic+, metastasis,
CA) neoplas+, anti-neoplastic) and (hyaluronic acid, mucopolysaccharide, glycosaminoglycan+)
Medline)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99/02151 A (HYAL PHARMACEUTICAL CORPORATION) 21 January 1999 Whole document	1-12
X	WO 98/17320 A (HYAL PHARMACEUTICAL CORPORATION) 30 April 1998 Whole document	1,3,4-9,11,12
X	US 5733891 A (AKIMA et al) 31 March 1998 Whole document	1-12

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" Document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 March 2000	14 APR 2000
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No.: (02) 6285 3929	Authorized officer **R.L. POOLEY** Telephone No.: (02) 6283 2242

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 00/00004

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Reg Cancer Treat (1994), 7, Klein et al, "Effects of hyaluronic acid on experimental tumour uptake of 5-Flurouracil", pages 163-164	1-12
P,X	Bioconjugate Chemistry, (1999), 10, Luo et al, "Synthesis and Selective Cytotoxicity of Hyaluronic Acid-Antitumour Bioconjugate, pages 755-763	1-12
X	American Chemical Society Symposium Series, 469 (Polymeric Drugs and Drug Delivery Systems), Ouchi et al, "Design of Polysaccharide-5-Fluorouracil Conjugates Exhibiting Antitumour Activities", pages 71-83	1-12
X	CA 1227427 A (LANDSBERGER) 29 September 1987 Whole document	5,12
X	WO 91/04058 A (NORPHARMACO INC) 4 April 1991 Whole document	1-12
X	WO 96/06622 A (HYAL PHARMACEUTICAL CORPORATION) 7 March 1996 Whole document	1,3,5
X	CA 2089621 A (NORPHARMACO INC) 17 August 1994 Whole document	1,2
A	WO 98/23648 A (SOCIETA' COOPERATIVA CENTRO RICHERCHE POLY-TECH A RESPONSABILITA' LIMITATA) 4 June 1998	

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 00/00004

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	99/02151	AU	82031/98	CA	2208924		
WO	98/17320	EP	952855	WO	96/06622	US	5827834
		US	5614506	US	5792753	US	5817642
		US	5817644	US	5824658	US	5834444
		US	5910489	US	5962433	US	5972906
		US	5977088	US	5990095	US	6017900
		US	6022866	WO	94/07505	WO	95/26193
		WO	95/29683	WO	95/30423	US	5811410
		US	5830882	US	5852002	AU	72721/96
		AP	618	AU	31595/95	CA	2145605
		CN	1130532	EP	778776	HU	76846
		CA	2131130	ZA	9507223	AP	175
		AU	64330/90	AU	52274/93	AU	14850/97
		BR	9006924	CA	2042034	CN	1051503
		EP	445255	EP	656213	HK	447/97
		HU	64699	HU	9500656	IN	171745
		LT	1582	NO	911952	SG	49658
		US	5914314	US	5929048	US	5932560
		US	5985850	US	5985851	WO	91/04058
		WO	91/04058	ZA	9007564	US	5639738
		US	5914322	US	5942498	US	5990096
		AP	448	AU	70224/96	BR	9307221
		CA	2079205	CN	1092654	CZ	9500662
		EP	661981	HK	353/97	HU	9500651
		HU	73637	MD	960294	MX	9305887
		NO	951122	NZ	255978	PL	308201
		SG	48845	SK	368/95	ZA	9307068
		AU	23008/95	EP	758246	CA	2122551
		AP	476	AU	34889/93	AU	42732/97
		CA	2061566	EP	626864	HU	70440

CONTINUED

INTERNATIONAL SEARCH REPORT

Patent Document Cited in Search Report		Patent Family Member					
		HU	9500650	MX	9300905	NZ	249072
		SG	49874	WO	93/16733	ZA	9301174
		AU	64222/94	AU	24023/95	CA	2122519
		CN	1151118	CZ	9603089	EP	760667
		HU	75868	SK	1379/96	AP	475
		AU	34888/93	CA	2061703	CN	1084064
		EP	626863	FI	943789	HU	9500652
		HU	75089	MD	960307	MX	9300904
		NO	943044	NZ	249071	SG	52416
		WO	93/16732				
US	5733891	AU	87140/91	CA	2070672	EP	506976
		WO	92/06714				
CA	1227427	NONE					
WO	91/04058	AP	175	AU	64330/90	AU	52274/93
		AU	14850/97	BR	2042034	CN	1051503
		EP	445255	EP	656213	HK	447/97
		HU	64699	HU	9500656	IN	171745
		LT	1582	NO	911952	SG	49658
		US	5811410	US	5827834	US	5830882
		US	5852002	US	5914314	US	5929048
		US	5932560	US	5985850	US	5985851
		ZA	9007564	US	5910489	US	5824658
		US	5962433	US	5614506	US	5792753
		US	5817642	US	5817644	US	5834444
		US	5972906	US	5977088	US	5990095
		US	6017900	US	6022866	WO	94/07505
		WO	95/26193	WO	95/29683	WO	95/30423
		US	5639738	US	5914322	WO	93/16733
		AU	34889/93	EP	626864	AP	476
		AU	42732/97	CA	2061566	HU	70440
		HU	9500650	MX	9300905	NZ	249072
		SG	49874	ZA	9301174	AU	72721/96
		CA	2131130	ZA	9507223	US	5942498
		US	5990096	AP	448	AU	70224/96
		BR	9307221	CA	2079205	CN	1092654
		CZ	9500662	EP	661981	HK	353/97

CONTINUED

INTERNATIONAL SEARCH REPORT

Patent Document Cited in Search Report		Patent Family Member					
		HU	9500651	MD	960294	MX	9305887
		NO	951122	NZ	255978	PL	308201
		SG	48845	SK	368/95	ZA	9307068
		AU	23008/95	EP	758246	CA	2122551
		AU	64222/94	AU	244023/95	CA	2122519
		CN	1151118	CZ	760667	HU	75868
		SK	1379/96	AP	475	AU	34888/93
		CA	2061703	CN	1084064	EP	626863
		FI	943789	HU	9500652	HU	75089
		MD	960307	MX	9300904	NO	943044
		NZ	249071	SG	52416	WO	93/16732
WO	96/06622	EP	952855	US	5827834	US	5614506
		US	5792753	US	5817642	US	5817644
		US	5824658	US	5834444	US	5910489
		US	5962433	US	5972906	US	5977088
		US	5990095	US	6017900	US	6022866
		WO	94/07505	WO	95/26193	WO	95/29683
		WO	95/30423	WO	98/17320	US	5811410
		US	5830882	US	5852002	AP	618
		AU	31595/95	CA	2131130	CN	1130532
		EP	778776	HU	76846	ZA	9507223
		CA	2145605	AU	72721/96	AP	175
		AU	64330/90	AU	52274/93	AU	14850/97
		BR	9006924	CA	2042034	CN	10511503
		EP	445255	EP	656213	HK	447/97
		HU	9500656	IN	171745	LT	1582
		NO	911952	SG	49658	US	5914314
		US	5929048	US	5932560	US	5985850
		US	5985851	WO	91/04058	ZA	9007564
		US	5639738	US	5914322	US	5942498
		US	5990096	AP	448	AU	70224/96
		BR	9307221	CA	2079205	CN	1092654
		CZ	9500662	EP	661981	HK	353/97
		HU	9500651	HU	73637	MD	960294
		MX	9305887	NO	951122	NZ	255978
		PL	308201	SG	48845	SK	368/95

CONTINUED

INTERNATIONAL SEARCH REPORT

Patent Document Cited in Search Report		Patent Family Member					
		ZA	9307068	AU	23008/95	EP	758246
		CA	2122551	AP	476	AU	34889/93
		AU	42732/97	CA	2061566	EP	626864
		HU	70440	HU	9500650	MX	9300905
		NZ	249072	SG	49874	WO	93/16733
		ZA	9301174	AU	64222/94	AU	24023/95
		CA	2122519	CN	1151118	CZ	9603089
		EP	760667	HU	75868	SK	1379/96
		AP	475	AU	34888/93	CA	2061703
		CN	1084064	EP	626863	FI	943789
		HU	9500652	HU	75089	MD	960307
		MX	9300904	NO	943044	NZ	249071
		SG	52416	WO	93/16732		
CA	2089621	NONE					
WO	98/23648	AU	57515/98	EP	941253	IT	962505

END OF ANNEX

CUSTOMS DECLARATION

DATE: 22/6/01

SENDER'S NAME: DR STUART BOYER
COMPANY NAME: GRIFFITH HACK
ADDRESS: LEVEL 3, 509 ST KILDA ROAD
MELBOURNE VICTORIA 3004 AUSTRALIA
PHONE: 613 92438300

RECEIVER'S NAME:
COMPANY NAME:
ADDRESS:

PHONE:

CONTENTS OF PACKAGE

DESCRIPTION OF CONTENTS	COUNTRY OF MANUFACTURE	NUMBER OF ITEMS	VALUE PER ITEM	TOTAL VALUE
COMPUTER DISK		1	$5.00	$5.00

TOTAL VALUE OF PACKAGE: $5.00

HAZARDOUS GOODS: YES / (NO)
NUMBER OF PACKAGES: 1 AIRWAYBILL NO:
REASON FOR SENDING: PATENT FILING

The above information is true and correct to the best of my knowledge.

PRINT NAME: STUART BOYER SIGNATURE:

DATE: 22/6/01

Please attach the original and 3 copies with the consignment note. Please ensure all fields are completed to avoid delay in shipping.

FORM40

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

GRIFFITH HACK
Level 3
509 St Kilda Road
Melbourne, VIC 3004
AUSTRALIE

GRIFFITH HACK
13 APR 2000
1 ~~for KS~~
2 SJB
3

Date of mailing (day/month/year) 31 March 2000 (31.03.00)	
Applicant's or agent's file reference FP12072	**IMPORTANT NOTIFICATION**
International application No. PCT/AU00/00004	International filing date (day/month/year) 06 January 2000 (06.01.00)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 13 January 1999 (13.01.99)
Applicant MEDITECH RESEARCH LIMITED et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
13 Janu 1999 (13.01.99)	PP 8131	AU	01 Marc 2000 (01.03.00)
09 Nove 1999 (09.11.99)	PQ 3938	AU	29 Febr 2000 (29.02.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Marc Salzman

Telephone No. (41-22) 338.83.38

003202208

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority should be indicated by the applicant on the line below.

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference
International application No. PCT/AU00/00004	International filing date *(day/month/year)* 6 JANUARY 2000	(Earliest) Priority date *(day/month/year)* 13 JANUARY 1999

Title of invention

A COMPOSITION AND METHOD FOR THE ENHANCEMENT OF THE EFFICACY OF DRUGS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No.:
MEDITECH RESEARCH LIMITED LEVEL 1 STERLING HOUSE 8 PARLIAMENT HOUSE WEST PERTH, WESTERN AUSTRALIA 6005 AUSTRALIA	Facsimile No.: Teleprinter No.:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
AUSTRALIA	AUSTRALIA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DR TRACEY BROWN
DEPARTMENT OF MOLECULAR BIOLOGY AND BIOCHEMISTRY
MONASH UNIVERSITY
CLAYTON, VICTORIA 3168
AUSTRALIA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
AUSTRALIA	AUSTRALIA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/AU00/00004

Box No. III AGENT OR COMMON REPRESENTATIVE: OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GRIFFITH HACK
LEVEL 3
509 ST KILDA ROAD
MELBOURNE, VICTORIA 3004
AUSTRALIA

Telephone No.: +61 3 9243 8300

Facsimile No.: +61 3 9243 8333

Teleprinter No.:

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

[X] the international application as originally filed

the description
[ ] as originally filed
[ ] as amended under Article 34

the claims
[ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings
[ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

[X] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

International application No.
PCT/AU00/00004

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ nucleotide and or amino acid sequence listing in computer readable form
6. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

MEDITECH RESEARCH LIMITED

Vivien Santer

.....

VIVIEN SANTER, Patent Attorney
for and on behalf of the applicant

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

FP12072

PCT REQUEST

Original (for SUBMISSION) - printed on 30.03.2000 11:34:21 AM

0 0-1	For receiving Office use only International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4 0-4-1	Form - PCT/RO/101 PCT Request Prepared using	PCT-EASY Version 2.90 (updated 08.03.2000)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	Australian Patent Office (RO/AU)
0-7	Applicant's or agent's file reference	FP12072
I	Title of invention	A COMPOSITION AND METHOD FOR THE ENHANCEMENT OF THE EFFICACY OF DRUGS
II II-1 II-2 II-4 II-5 II-6 II-7	Applicant This person is: Applicant for Name Address: State of nationality State of residence	 applicant only all designated States except US MEDITECH RESEARCH LIMITED Level 1 Sterling House 8 Parliament House West Perth, Western Australia 6005 Australia AU AU
III-1 III-1-1 III-1-2 III-1-4 III-1-5 III-1-6 III-1-7	Applicant and/or inventor This person is: Applicant for Name (LAST, First) Address: State of nationality State of residence	 applicant and inventor US only BROWN, Tracey Department of Molecular Biology and Biochemistry Monash University Clayton, Victoria 3168 Australia AU AU

FP12072

PCT REQUEST

Original (for SUBMISSION) - printed on 30.03.2000 11:34:21 AM

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name	GRIFFITH HACK
IV-1-2	Address:	Level 3 509 St Kilda Road Melbourne, Victoria 3004 Australia
IV-1-3	Telephone No.	+61 3 9243 8300
IV-1-4	Facsimile No.	+61 3 9243 8333
IV-1-5	e-mail	ghmelb@griffithhack.com.au
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY CA CH&LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

PCT REQUEST

FP1207

Original (for SUBMISSION) - printed on 30.03.2000 11:34:21 AM

V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	13 January 1999 (13.01.1999)	
VI-1-2	Number	PP8131	
VI-1-3	Country	AU	
VI-2	Priority claim of earlier national application		
VI-2-1	Filing date	09 November 1999 (09.11.1999)	
VI-2-2	Number	PQ3938	
VI-2-3	Country	AU	
VI-3	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1, VI-2	
VII-1	International Searching Authority Chosen	Australian Patent Office (ISA/AU)	
VIII	Check list	number of sheets	electronic file(s) attached
VIII-1	Request	4	-
VIII-2	Description	88	-
VIII-3	Claims	2	-
VIII-4	Abstract	1	fp12072.txt
VIII-5	Drawings	28	-
VIII-7	TOTAL	123	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	Figure of the drawings which should accompany the abstract	7	
VIII-19	Language of filing of the international application	English	
IX-1	Signature of applicant or agent	Vivien Santer	
IX-1-1	Name	GRIFFITH HACK	
IX-1-2	Name of signatory	Vivien Santer	

PCT REQUEST

FP12072

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IX-2	Signature of applicant or agent	
IX-2-1	Name	MEDITECH RESEARCH LIMITED
IX-3	Signature of applicant or agent	
IX-3-1	Name (LAST, First)	BROWN, Tracey

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10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/AU
10-6	Transmittal of search copy delayed until search fee is paid	

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11-1	Date of receipt of the record copy by the International Bureau	

ATENT COOPERATION TREAT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference SJB:AN:FP12072	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
International Application No. **PCT/AU00/00004**	International Filing Date *(day/month/year)* 6 January 2000	Priority Date *(day/month/year)* 13 January 1999
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] A61K 47/36, A61P.35/00		
Applicant MEDITECH RESEARCH LIMITED et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

[X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of **2** sheet(s).

3. This report contains indications relating to the following items:

I	[X]	Basis of the report
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[X]	Certain documents cited
VII	[ ]	Certain defects in the international application
VIII	[X]	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
14 July 2000	1 May 2001
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **R.L. POOLEY** Telephone No. (02) 6283 2242

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU00/00004

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-88**, as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **89-90,** received on **19 April 2001** with the letter of **18 April 2001**

☒ the drawings, pages **1-28,** as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, was on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **1-8**	**YES**
	Claims **9**	**NO**
Inventive step (IS)	Claims **1-7**	**YES**
	Claims **8, 9**	**NO**
Industrial applicability (IA)	Claims **1-9**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

D1 - WO 98/17320 A

D2 - US 5733891 A

D3 - Reg Cancer Treat (1994), 7, Klein et al, pages 163-164

D4 - American Chemical Society Symposium Series, 469, Ouchi et al, pages 71-83

D5 - CA 1227427 A

D6 - WO 91/04058 A

D7 - WO 96/06622 A

D8 - CA 2089621 A

NOVELTY (N) Claim 9

Documents D1, D6 and D7 all disclose cytotoxic compositions that contain hyaluronan having a molecular weight of greater than 700,000 Daltons and a cytotoxic agent. These compositions would all be capable of being used for reducing or overcoming acquired or inherent cellular resistance. All of these documents envisage the systemic administration of the compositions and describe some form of enhanced effectiveness of the cytotoxic agents. These documents are therefore considered to anticipate the embodiment of claim 9. Your submissions in relation to these documents indicate that they do not disclose the use of hyaluronan to overcome cellular resistance to cytotoxic agents. However the above claim is construed whereby the compositions are not restricted to this use and are only required to be capable of the defined use. It is considered that compositions disclosed in the above documents would inherently have the required capability, and therefore anticipate claim 9. The applicant's submissions in relation to the disclosure of document D2 suggest that the compositions of this document would not have the required capability due to the covalent bonding between the hyaluronan and the cytotoxic agent. In view of these submissions, this document is no longer considered to anticipate claim 9.

None of the documents D1-D8 disclose the use of hyaluronan and cytotoxic agents in the treatments of claims 1 to 8. Consequently these claims are considered to be novel over the disclosures of these documents.

INVENTIVE STEP (IS) Claims 8, 9

Claim 9: as above

Claims 8, 9: Documents D3 and D4 both disclose cytotoxic compositions that contain hyaluronan and a cytotoxic agent, although they do not disclose the use of hyaluronan having the molecular weight specified in claim 9. However the present description does not describe hyaluronan having a molecular weight of greater than 700,000 Daltons as providing any technical advantages over hyaluronan having other molecular weights.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date (valid claim) *(day/month/year)*
P,X WO 99/02151 A	21 January 1999	8 July 1998	9 July 1997

2. Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure *(day/month/year)*	Date of written disclosure referring to non-written disclosure *(day/month/year)*

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

(i) Claim 8 is unclear in that there is no antecedent for "said agent" in line 4 of the claim and as a consequence, the entity having reduced gastrointestinal toxicity is unclear.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V

Additionally, the description does not specifically distinguish hyaluronan having the specified molecular weight over other forms of hyaluronan. The cited documents all disclose the systemic administration of a composition containing hyaluronan and a cytotoxic agent, as well the binding of hyaluronan to receptors on tumour cells and the uptake of the cytotoxic agent by the cells. Consequently the compositions of these citations are considered to possess the functional capability defined in claim 9 and therefore to be the technical equivalent of the compositions currently defined in claim 9.

Additionally, documents D2 and D4 indicate that the formulations of hyaluronan and cytotoxic agent provide reduced side effects, and gastrointestinal toxicity is a well known side effect of cytotoxic drugs such as paclitaxel. Consequently claim 8 is considered to lack inventive step in view of the disclosures of this document. The applicant's submissions in relation to document D2 indicate that the compositions of this document would not be capable of reducing or overcoming acquired or inherent cellular resistance due to covalent bonding between the agent and hyaluronan. However the formulation of the citation is stated to suppress harmful side effects of the medicinal agents and gastrointestinal toxicity is a well known side effect of cytotoxic agents such as paclitaxel and fluorouracyl.

The treatments of cellular resistance defined in claims 1-7 are considered to be inventive over the disclosures of documents D1-D8.

INDUSTRIAL APPLICABILITY (IA)

Claims 1-9 are considered to possess industrial applicability. Please note that claims 1-8 are directed to subject matter of Rule 67.1 (methods of treatment of humans and animals) and as such do not require an international preliminary examination. However, because the subject matter does not contravene Australian Patent Law, these claims have been considered.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A1

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761,104 17 September 1991 (17.09.91) US

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(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

Published
With international search report.

(54) Title: COMPOSITIONS CONTAINING QUINOLONE ANTIBIOTICS AND SULFONATE OF POLYSTYROL

(57) Abstract

Aqueous pharmaceutical compositions containing a synergistic combination of a quinolone and a polystyrene sulfonic acid polymer are described, wherein the compositions are clear solutions which are comfortable and have sustained release. Methods for use of the compositions are also disclosed. This type of formulation is particularly useful with ciprofloxacin-type quinolones by greatly increasing the solubility of these quinolones, making it feasible to have aqueous solutions containing such quinolones at or near physiological pH.

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COMPOSITIONS CONTAING QUINOLONE ANTIBIOTICS AND SULFONATE OF POLYSTYROL

Background of the Invention

The present invention relates to pharmaceutical compositions comprising a synergistic combination of a quinolone and a polystyrene sulfonic acid polymer. In particular, the present invention relates to aqueous preparations containing a quinoline and a polystyrene sulfonic acid polymer, wherein the quinoline is solubilized by the polystyrene sulfonic acid polymer. These preparations are particularly well-suited for ophthalmic or otic use in the treatment of bacterial infections.

A number of quinolones have previously been used to treat bacterial infections through a variety of methods, including topical administration. Representative quinolones and antibacterial compositions thereof are: the norfloxacin-type quinolones, disclosed in U.S. Patents Nos. 4,146,719 (Irikura) and 4,292,317 (Pesson); the ofloxacin-type quinolones, disclosed in U.S. Patent No. 4,382,892 (Hayakaw, et al.); and the ciprofloxacin-type quinolones, disclosed in U.S. Patent No. 4,670,444 (Grohe, et al.). The ciprofloxacin-type quinolones generally have a broader spectrum of antibacterial activity than either of the other types of quinolones listed above. Because of the poor solubility of these quinolones at physiological or higher pH, the ciprofloxacin-type quinolone formulations were developed at acidic pH and/or as suspensions; however, when these formulations were administered topically to the eye, they were uncomfortable.

Summary of the Invention

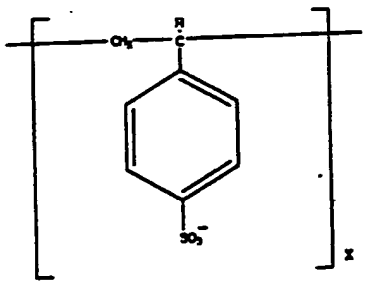
The present invention provides aqueous pharmaceutical compositions and methods for the treatment of bacterial infections using these compositions. The compositions are particularly well-suited for ocular or otic use. The compositions of the present invention are formulated such that the solubility of quinolones and/or quinolone analogues at higher pH

is increased by the use of an ionic polymer (namely, polystyrene sulfonic acid polymer) which binds the quinolone to the polymer. The binding between the polymer and the quinolone additionally provides both initial and continual comfort upon instillation to the eye, as there is less free drug to irritate the tissues of the eye. Another added benefit to the compositions of the present invention is that there is sustained release of the quinolone.

Detailed Description of the Invention

The pharmaceutical compositions of the present invention contain a synergistic combination of a quinolone and/or quinolone analogue having antibacterial activity and a polystyrene sulfonic acid polymer, preferably at physiological or near-physiological pH. For purposes of this specification, quinolones and/or quinolone analogues shall hereinafter be collectively referred to as "quinolone" or "quinolones" unless otherwise stated. These compositions are especially useful in the eye, as the compositions are comfortable upon topical administration to the eye and provide sustained release of the quinolone.

The polystyrene sulfonic acid polymers (and their salts) which are used in the formulations of the present invention have the following formula:



wherein,

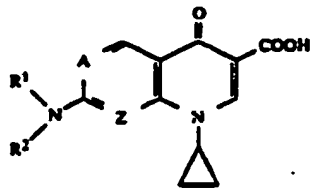
R = H or CH_3; and

X = an integer such that the molecular weight of the polystyrene sulfonic acid polymer may vary from about 10,000 to 1.6 million.

In the preferred polystyrene sulfonic acid of the above formula, R=H and the molecular weight is between about 500,000 to about 1,000,000, preferably about 600,000. The polystyrene sulfonic acid polymers are used in the formulas of the present invention at a concentration less than about 8.0 by weight (wt%), preferably less than about 5.0 wt%.

All quinolones having antibacterial activity and which are ophthalmically acceptable are useful in the compositions of the present invention, including, but not limited to the quinolones disclosed in U.S. Patents Nos. 4,146,719 (Kyorin), 4,292,317 (Bellon), 4,382,892 (Daiichi), 4,670,444 (Grohe, et al.). The entire contents of these patents are hereby incorporated by reference herein.

The preferred quinolones useful in the compositions of the present invention are the type disclosed in U.S. Patent No. 4,670,444 referenced above. The quinolones described therein are generally described as 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline- and -naphthyridine-3-carboxylic acids of the formula:



(I)

or a pharmaceutically acceptable acid addition salt or an alkali or alkaline earth metal salt thereof,

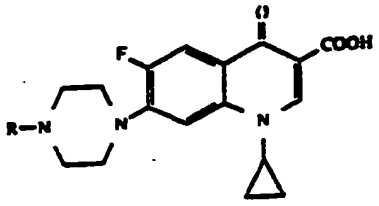
in which A represents a nitrogen atom or CR_3,

wherein R_3 denotes a hydrogen, a nitro group or a halogen atom, or a carboxamide or carboxyl group, and

Z represents a nitrogen atom or C-H, and A and Z cannot simultaneously be nitrogen atoms, and R_1 and R_2 are identical or different and represent a hydrogen atom or a straight-chain or branched alkyl, alkenyl, or alkinyl radical which has up to 12 carbon atoms and is optionally substituted by radical(s) selected from

hydroxyl, alkoxy, alkylmercapto or dialkylamino with 1 to 3 carbon atoms in each alkyl radical, alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or bi-cyclic carbocyclic aryl, or furthermore represents a cylcloalkyl radical with 3 to 6 carbon atoms, or, together with the nitrogen atom which they substituted or together with a further hetero-atom selected from the group consisting of N, O and S form a 3-membered to 7-membered ring which can be substituted by radical(s) selected from alkyl or alkenyl with 1 to 6 carbon atoms, hydroxyl, alkoxy or alkylmercapto with 1 to 3 carbon atoms, alkoxy carbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or bi-cyclic carbocyclic aryl.

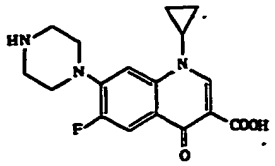
More preferred are the 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acids of the formula:



(II)

or salts and/or hydrates thereof, in which R denotes hydrogen, methyl, ethyl or β-hydroxyethyl.

Most preferred is ciprofloxacin, which has the following structure:



The chemical name for ciprofloxacin is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid.

Methods of preparation for the preferred quinolones are described in U.S. 4,670,444. The quinolone component of the pharmaceutical compositions

of the present invention generally contain less than about 1.0 wt% of the total composition, preferably between about 0.1 wt% to about 0.75 wt%. The most preferred quinolone concentration is between about 0.2 to about 0.4 wt%.

The compositions of the present invention are prepared by combining the quinolone with polystyrene sulfonic acid polymer in aqueous media and adjusting the pH, if necessary. The compositions of the present invention may also include one or more ingredients conventionally found in ophthalmic or otic formulations, such as preservatives (e.g., benzalkonium chloride or thimerosal), viscosity-imparting agents (e.g., polyvinyl alcohol or hydroxyprovomethylcellulose) and tonicity agents (e.g., sodium chloride or mannitol). The compositions will also normally include buffering agents, such as phosphates and citrates, to maintain the pH within the range of physiological pH (pH between 6.0 and 7.5) and tonicity agents, such as mannitol. Hydrochloric acid or sodium hydroxide will typically be used to adjust the pH of the resultant composition.

The following example is presented to illustrate further certain preferred embodiments of the present invention and should not be interpreted as limiting the scope of the invention in any way.

EXAMPLE

The following represents a preferred embodiment of the compositions of the present invention.

Ingredient	Amount(wt%)
Ciprofloxacin HCl, Monohydrate	0.35*
PSSA	50 ml**
Mannitol	3.75
Benzalkonium chloride	0.01
NaOH and/or HCl	to pH 7.0
Purified Water	Q.S.

*Equivalent to 0.3% as base
**2% PSSA solution in water

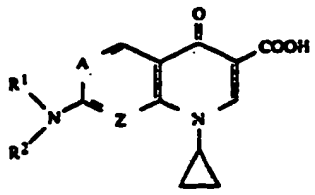
The 2% PSSA solution was filtered through a 0.6 micron filter, 50 milliliters (ml) of the filtered solution added to a first beaker, and the contents stirred. To a second beaker were added 15 ml of water and the ciprofloxacin and the mixture stirred until the ciprofloxacin was completely dissolved, at which point the mannitol and benzalkonium chloride were added and the contents stirred again, until a homogeneous solution was achieved. Then the contents of the second beaker were slowly added to the contents of the first beaker, while stirring. The pH was then adjusted to pH 7.0 using NaOH and water was added to bring the volume of the final solution to 100 ml.

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is Claimed is:

1. An aqueous pharmaceutical composition useful in the treatment of bacterial infections which comprises a quinolone and a polystyrene sulfonic acid polymer.

2. The composition of claim 1, wherein the quinolone has the following formula:



or a pharmaceutically acceptable acid addition salt or an alkali or alkaline earth metal salt thereof,

in which A represents a nitrogen atom or CR_3;

wherein R_3 denotes a hydrogen, a nitro group or a halogen atom, or a carboxamide or carboxyl group; and

Z represents a nitrogen atom or C-H, and A and Z cannot simultaneously be nitrogen atoms, and R_1 and R_2 are identical or different and represent a hydrogen atom or a straight-chain or branched alkyl, alkenyl, or alkinyl radical which has up to 12 carbon atoms and is optionally substituted by radical(s) selected from hydroxyl, alkoxy, alkylmercapto or dialkylamino with 1 to 3 carbon atoms in alkyl radical, alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or by-cyclic carbocyclic aryl, or furthermore represents a cylcloalkyl radical with 3 to 6 carbon atoms, or, together with the nitrogen atom which they substituted or together with a further hetero-atom selected from the group consisting of N, O and S form a 3-membered to 7-membered ring which can be substituted by radical(s) selected from alkyl or alkenyl with 1 to 6 carbon atoms, hydroxyl, alkoxy or alkylmercapto with 1 to 3 carbon atoms, alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or bi-cyclic carbocyclic aryl.

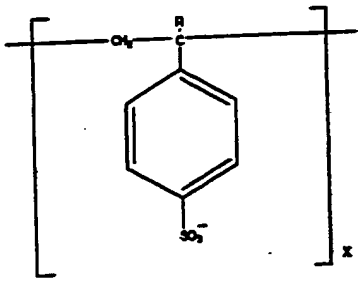
3. The aqueous pharmaceutical composition of claim 1, wherein the quinolone is present at a concentration less than or equal to about 1.0 wt%.

4. The aqueous pharmaceutical composition of claim 3, wherein the quinolone is present at a concentration between about 0.1 wt% to about 0.75 wt%.

5. The aqueous pharmaceutical composition of claim 4, wherein the quinolone is present at a concentration between about 0.2 to about 0.4 wt%.

6. The aqueous pharmaceutical composition of claim 5, wherein the quinolone is present at a concentration of about 0.3 wt%.

7. The aqueous pharmaceutical composition of claim 1, wherein the polystyrene sulfonic acid polymer has the following formula:

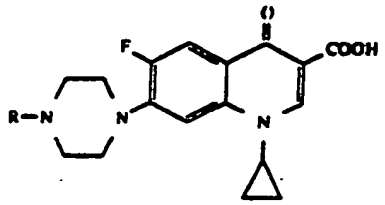


wherein: R = H or CH_3; and X = an integer such that the molecular weight of the polystyrene sulfonic acid polymer may vary from about 10,000 to 1.6 million.

8. The aqueous pharmaceutical composition of claim 7, wherein the concentration of the polystyrene sulfonic acid polymer is less than or equal to about 8.0 wt%.

9. The aqueous pharmaceutical composition of claim 7, wherein the concentration of the polystyrene sulfonic acid polymer is less than or equal to about 5.0 wt%.

10. An aqueous pharmaceutical composition useful in the treatment of bacterial infections consisting essentially of a quinolone of formula:



or salts and/or hydrates thereof, in which R denotes hydrogen, methyl, ethyl or β-hydroxyethyl; and a polystyrene sulfonic acide polymer.

11. The aqueous pharmaceutical composition of claim 10, wherein the quinolone is present at a concentration less than or equal to about 1.0 wt%.

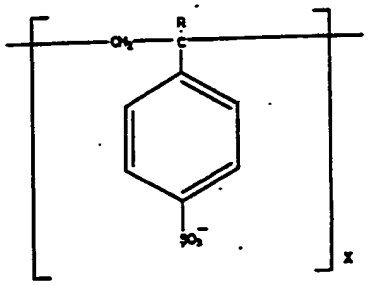
12. The aqueous pharmaceutical composition of claim 11, wherein the quinolone is present at a concentration between about 0.1 wt% to about 0.75 wt%.

13. The aqueous pharmaceutical composition of claim 12, wherein the quinolone is present at a concentration between about 0.2 to about 0.4 wt%.

14. The aqueous pharmaceutical composition of claim 13, wherein the quinolone is present at a concentration of about 0.3 wt%.

15. The aqueous pharmaceutical composition of claim 12, wherein the quinolone is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piprazinyl)-3-quinoline carboxylic acid.

16. The aqueous pharmaceutical composition of claim 10, wherein the polystyrene sulfonic acid polymer has the following formula:



wherein: R = H or CH_3; and X = an integer such that the molecular weight of the polystyrene sulfonic acid polymer may vary from about 10,000 to 1.6 million.

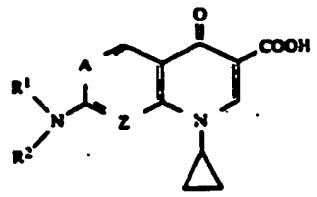
17. The aqueous pharmaceutical composition of claim 16, wherein the concentration of the polystyrene sulfonic acid polymer is less than or equal to about 8.0 wt%.

18. The aqueous pharmaceutical composition of claim 16, wherein the concentration of the polystyrene sulfonic acid polymer is less than or equal to about 5.0 wt%.

19. The aqueous pharmaceutical composition of claim 10, wherein the quinolone is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piprazinyl)-3-quinoline carboxylic acid.

20. A method for the treatment of bacterial infections which comprises the topical administration of an aqueous pharmaceutical composition which comprises a quinolone and a polystyrene sulfonic acid polymer.

21. The method of claim 20, wherein the quinolone has the following formula:



or a pharmaceutically acceptable acid addition salt or an alkali or alkaline earth metal salt thereof,

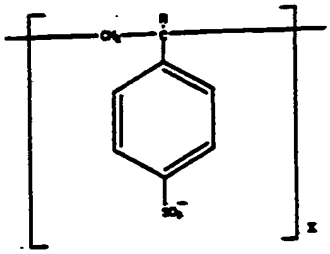
in which A represents a nitrogen atom or CR_3;

wherein R_3 denotes a hydrogen, a nitro group or a halogen atom, or a carboxamide or carboxyl group; and

Z represents a nitrogen atom or C-H, and A and Z cannot simultaneously be nitrogen atoms, and R_1 and R_2 are identical or different and represent a hydrogen atom or a straight-chain or branched alkyl, alkenyl, or alkinyl radical which has up to 12 carbon atoms and is optionally substituted by radical(s) selected from hydroxyl, alkoxy, alkylmercapto or dialkylamino with 1 to 3 carbon atoms in alkyl radical, alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or by-cyclic carbocyclic aryl, or furthermore represents a cylcloalkyl radical with 3 to 6 carbon atoms, or, together with the nitrogen atom which they substituted or together with a further hetero-atom selected from the group consisting of N, O and S form a 3-membered to 7-membered ring which can be substituted by radical(s) selected from alkyl or alkenyl with 1 to 6 carbon atoms, hydroxyl, alkoxy or alkylmercapto with 1 to 3 carbon atoms, alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or bi-cyclic carbocyclic aryl.

22. The method of claim 20, wherein the quinolone is present at a concentration less than or equal to about 1.0 wt%.

23. The method of claim 20, wherein the polystyrene sulfonic acid polymer has the following formula:



wherein: R = H or CH_3; and X = an integer such that the molecular weight of the polystyrene sulfonic acid polymer may vary from about 10,000 to 1.6 million.

24. The method of claim 23, wherein the concentration of the polystyrene sulfonic acid polymer is less than about 8.0 wt%.

INTERNATIONAL SEARCH REPORT

PCT/US 92/07744

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K47/48

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0 295 495 (BAYER AG) 21 December 1988 see claims see examples see page 3, line 26 - line 44 see page 4, line 47 - line 51 see page 5, line 12 - line 16	1-24

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
23 NOVEMBER 1992	07. 12. 92
International Searching Authority	**Signature of Authorized Officer**
EUR PEAN PATENT FFICE	SCARPONI U.

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9207744 SA 64895

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 23/11/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0295495	21-12-88	DE-A-	3719764	22-12-88
		AU-B-	599239	12-07-90
		AU-A-	1764388	15-12-88
		DE-A-	3865748	28-11-91
		JP-A-	1004625	09-01-89